

MF2
Cont
[altering, relative to the cell in the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii)] increasing the rate of survival of the neuronal cells.

DI
Cont
50. (amended) A method for [modulating one or more of] promoting growth[, differentiation and survival] of [a] mammalian neuronal stem cells [in an animal], comprising [administering to the animal a therapeutically] treating the cell with an effective amount of a *hedgehog* polypeptide to [alter, relative to the absence of *hedgehog* treatment, at least one of (i)] increase the rate of growth of the neuronal stem cells[, (ii) differentiation, or (iii) survival of one or more cell-types in said animal].

Please cancel claims 51-54 without prejudice.

55. (amended) The method of claim [54] 56, wherein said disorder is [Alzheimer's Disease or] Parkinson's Disease.

56. (amended) A method [of] for preventing, treating or reducing the severity of a neurodegenerative disorder, comprising administering to [said] a subject a therapeutically effective amount of a *hedgehog* polypeptide [to alter, relative to the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more cell-types in said subject].

DI
57. (amended) The method of claim 56, wherein said disorder is selected from the group consisting of Alzheimer's [Parkinson's] Disease, Huntington's Disease, Pick's Disease, Ballism, Guillain-Barre Syndrome, Amyotrophic Lateral Sclerosis, spinocerebellar degenerations, and [chronic] peripheral neuropathy.

58. (amended) The method of claim 57, wherein said neurodegenerative disorder includes loss of neuronal cells [are] selected from the group consisting of cholinergic neurons, GABAergic neurons [or] and striatal neurons.

59. (amended) A method [of] for preventing, treating or reducing the severity of an acute, subacute or chronic injury to the nervous system in a subject, comprising administering to a

22
subject a therapeutically effective amount of a *hedgehog* polypeptide to alter, relative to the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more neuronal cell-types in said subject.

60. (reiterated) The method of claim 59, wherein said injury is selected from the group consisting of traumatic injury, chemical injury, ~~vasal~~ injury, ~~vasal~~ deficit, infectious injury, inflammatory injury and tumor-induced injury.

23
61. (amended) The method of claim 60 wherein said [inflammatory] injury is a result of a chronic inflammatory disease.

62. (reiterated) The method of claim 61, wherein said inflammatory disease is multiple sclerosis.

63. (amended) The method of claim 60, wherein said [vasal] injury [is] includes ischemia of neuronal tissue [resulting from a stroke].

24
64. (amended) The method of claim 63, wherein said injury includes ischemia resulting from a stroke [A method for preventing the degeneration or premature death of neuronal cells in a subject, comprising administering to said subject neuronal cells which have been contacted with an effective amount of a *hedgehog* polypeptide, thereby altering, relative to the cell in the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of said neuronal cell].

65. (amended) The method of claim [64] 49, wherein said [administered] neuronal cells are introduced into a subject by cerebral grafting.

66. (amended) The method of claim 65, wherein said [administered] neuronal cells are derived from fetal or neonatal animals

67. (amended) The method of claim 64, wherein said [administered] neuronal cell is a neuronal stem cell.

68. (reiterated) The method of claim ~~67~~ wherein said neuronal stem cell is a neural crest cell.

DS
MF3
69. (amended) The method of claim 1, 49, 50, [54,] 56 or 59, wherein said *hedgehog* protein is administered in combination with one or more other neurotrophic factors.

70. (reiterated) The method of claim 69, wherein said other neurotrophic factor is selected from the group consisting of CNTF, BDNF and NGF.

71. (amended) The method of claim ~~36~~ [A method of preventing, treating or reducing the severity of a] wherein the neurodegenerative disorder includes degeneration of the peripheral nervous system [in a subject, comprising administering to a subject a therapeutically effective amount of a *hedgehog* polypeptide to alter, relative to the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more cell-types in said animal].

72. (reiterated) The method of claim 71, wherein said disorder affects smooth muscle tissue and endocrine tissue, such as glandular tissue.

73. (reiterated) The method of claim ~~72~~ wherein said disorder is tachycardia or atrial cardiac arrhythmia.

74. (reiterated) The method of claim ~~71~~ wherein said disorder affects sensory or motor neurons.

D
75. (amended) The method of claim 74, wherein said disorder is selected from the group consisting of [CNS,] trauma, infarction, infection, metabolic disease, nutritional deficiency, toxic agents and chronic pain syndrome.

76. (reiterated) The method of claim 1, wherein said neuronal cell is a neural progenitor cell.

77. (reiterated) The method of claim 1, wherein said neuronal cell differentiates into a cell having a particular neural phenotype, such as a neuron or a glia.
78. (reiterated) The method of claim 1, wherein said neuronal cell is in the central nervous system or the peripheral nervous system.
79. (reiterated) The method of claim 78, wherein said *hedgehog* treatment repairs central or peripheral nerve damage.
80. (reiterated) The method of claim 1, wherein said *hedgehog* polypeptide mimics the effect of a naturally-occurring *hedgehog* protein.
81. (reiterated) The method of claim 1, wherein said *hedgehog* polypeptide antagonizes the effects of a naturally-occurring *hedgehog* protein.

82. (amended) The method of claim 1, wherein said *hedgehog* polypeptide comprises an amino acid sequence identical or homologous with all or a portion of an amino acid sequence designated in one of SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:34[, SEQ ID NO:40 or SEQ ID NO:41].

83. (amended) The method of claim 1, 49, 50, 56 or 59, wherein said *hedgehog* polypeptide has an amino acid sequence which is encoded by a nucleic acid which hybridizes under highly stringent conditions to a [identical or homologous with all or a portion of a] nucleic acid sequence [designated in one of] selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 [or] and SEQ ID NO:7.

84. (reiterated) The method of claim 1, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 80% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7.

85. (*reiterated*) The method of claim 1, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 90% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7.

86. (*reiterated*) The method of claim 1, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 95% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7.

Please cancel claims 87-92 without prejudice.

93. (**amended**) The method of any one of claim 1 or 83, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 80 percent identical with a sequence selected from the group consisting of residues 104-189 of SEQ ID NO:8, residues 102-187 of SEQ ID NO:9, residues 31-116 of SEQ ID NO:10, residues 102-187 of SEQ ID NO:11, [and] or residues 101-186 of SEQ ID NO:12.

94. (**amended**) The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 70 percent identical with a sequence selected from the group consisting of residues 27-189 of SEQ ID NO:8, residues 22-187 of SEQ ID NO:9, residues 1-116 of SEQ ID NO:10, residues 25-187 of SEQ ID NO:11, [and] or residues 24-186 of SEQ ID NO:12.

95. (**amended**) The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 60 percent identical with an amino acid sequence selected from the group consisting of residues 27-425 of SEQ ID NO:8, residues 22-396 of SEQ ID NO:9, residues 1-336 of SEQ ID NO:10, residues 25-437 of SEQ ID NO:11, residues 24-418 of SEQ ID NO:12, or residues 24-475 of SEQ ID NO:13, residues 1-312 of SEQ ID NO:14[, and an extracellular fragment thereof of at least 50 amino acids].

96. (*reiterated*) The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence encoded by a naturally occurring vertebrate *hedgehog* gene.

97. (reiterated) The method of claim 96, wherein said *hedgehog* gene is a mammalian *hedgehog* gene.

98. (reiterated) The method of claim 97, wherein said *hedgehog* gene is a human *hedgehog* gene.

99. (reiterated) The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence which is encoded by at least a portion of a *hedgehog* gene of vertebrate origin corresponding to residues 64-567 of SEQ ID NO:1, residues 64-561 of SEQ ID NO:2, residues 1-348 of SEQ ID NO:3, residues 73-561 of SEQ ID NO:4, and residues 70-558 of SEQ ID NO:5.

100. (reiterated) The method of claim 1, wherein said *hedgehog* amino acid sequence is represented in the general formula SEQ ID NO:41.

101. (reiterated) The method of claim 1, wherein said polypeptide has an approximate molecular weight of 19kD.

102. (reiterated) The method of claim 1, wherein said polypeptide includes at least 150 amino acid residues of the N-terminal half of a *hedgehog* protein.

Sub
Ct
D10 103. (Amended) The method of claim 1, wherein said polypeptide binds to a *patched* [protein] receptor.

104. (Amended) The method of claim 103, wherein said *patched* [protein] receptor is a *patched* [protein] receptor of a vertebrate organism

Please cancel claims 105 and 106 without prejudice.

D11 107. (amended) The method of claim 1 [106], wherein said neuronal cells are selected from the group consisting of motor neurons, cholinergic neurons, dopanergic neurons, serotenergic neurons and peptidergic neurons.